Remarks

Claims 57-86 are pending in the subject application. Applicants acknowledge that claims 84-86 have been withdrawn from further consideration as being drawn to a non-elected invention. By this Amendment, Applicants have canceled claims 63, 78, and 84-86, amended claims 57, 58, 60, 61, 64, 68, 69, 70, 71, 72, 73-76, and 79, and added new claims 87-89. Support for the amendments and new claims can be found throughout the subject specification and in the claims as originally filed. Entry and consideration of the amendments presented herein is respectfully requested. Accordingly, claims 57-62, 64-77, 79-83, and 87-89 are currently before the Examiner. Favorable consideration of the pending claims is respectfully requested.

Submitted herewith is a supplemental Information Disclosure Statement, accompanied by the form PTO/SB/08, and a copy of the Proudfoot *et al.* reference cited herein. Applicants respectfully request that the reference listed on the form PTO/SB/08 be considered and made of record in the subject application.

The Examiner has indicated that a new title of the invention is required because the word "novel" is not considered part of the title. Applicants have amended the title of the invention and request reconsideration and withdrawal of this objection.

Claims 57-83 are rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention. The Office Action argues that the as-filed specification fails to provide adequate written description for the claimed invention because the specification is alleged to not teach a sufficient number of polypeptides within the genus claimed via sequence identity and biological activity. The Office Action argues that the as-filed application fails to provide adequate written support for polypeptides having at least 70% identity to the polypeptides recited in claims 63 and 78 and that the claims do not require any particular conserved structure or other disclosed feature. Applicants respectfully submit that this issue is moot in view of the cancellation of the claims.

The Office Action also argues that the as-filed specification fails to provide adequate written support for polypeptides containing amino acid substitutions that are not alanine residues. As set forth in the Federal Register Vol. 66, No. 4, January 5, 2001, page 1106 right-hand column:

> (2) For each claim drawn to a genus: The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by [...] disclosure of relevant, identifying characteristic, *i.e.*, structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus [...] [...], there may be situations where one species adequately supports a genus. What constitutes a "representative number" is an inverse function of the skill and knowledge in the art.

Further, Court of Appeals for the Federal Circuit has held that "in accordance with our prior case law, that (1) examples are not necessary to support the adequacy of a written description; (2) the written description standard may be met (as it is here) even where actual reduction to practice of an invention is absent; and (3) there is no *per se* rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure".

In this case, the claims recite a biological macromolecule of known structure (human MCP-1), the amino acid positions at which substitutions are to be made and those amino acids that could be substituted at those positions (*e.g.*, see Tables 1 and 2 and page 9, lines 14-19, for example). Additionally, the as-filed specification contains an example of a polypeptide containing an additional amino acid substitution (see SEQ ID NO: 3, and page 11, lines 6-9). Thus, Applicants respectfully submit that the state of the art, at the time the instant application was filed, would support a view that substitution of the amino acids at positions 18 and 19, as numbered on the sequence of human mature MCP-1 (corresponding to amino acids 24-99 of SEQ ID NO: 1), would be considered representative of substitutions with glycine, serine, threonine, proline, aspartic acid, asparagine, glutamic acid or glutamine at these positions and that the as-filed specification contains an adequate written description of the claimed invention. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Claims 57-83 are rejected under 35 U.S.C. § 112, first paragraph, because the specification, while enabling for an isolated MCP-1 polypeptide comprising SEQ ID NO: 3, does not reasonably provide enablement for the MCP-1 polypeptides recited in claims 57 and 72 or the nucleic acids encoding such polypeptides. The Office Action argues that the as-filed specification fails to enable the claimed invention in that the claims are overly broad in their recitation of "at least 70%

homology with human mature MCP-1, MCP-2, MCP-3, MCP-4 or eotaxin" because no guidance is given as to which of the myriad of MCP-1 polypeptides will have the characteristics of the desired polypeptide. While the Office Action indicates such an activity to be as an antagonist of the MCP-1 receptor, Applicants respectfully submit that the activity recited in the claims relates to the ability of the claimed muteins to antagonize the activity of unaltered MCP-1 (see, for example, page 32, lines 1-10 of the as-filed specification). The Office Action further argues that no prophetic or actual examples on expected performance parameters of any of the possible variants have been disclosed and that it is known that the substitution of even a single amino acid residue in a protein can have dramatic effects on the protein's function. The Office Action further argues that there is no guidance in the specification as to how one skilled in the art is to produce the claimed muteins and concludes that undue experimentation would be required to practice the claimed invention. Applicants traverse.

Applicants also submit that nothing more than objective enablement is required, and therefore it is irrelevant whether this teaching is provided through broad terminology or illustrative examples. As the Court of Appeals for the Federal Circuit stated in *LizardTech, Inc. v. Earth Resource Mapping, PTY, Inc.* (*see* 424 F.3d 1336, 1345 (Fed.Cir.2005) (citing *Union Oil Co. v. Atl. Richfield Co.*, 208 F.3d 989, 997 (Fed.Cir.2000); *In re GPAC Inc.*, 57 F.3d 1573, 1579 (Fed.Cir.1995)):

> A claim will not be invalidated on section 112 grounds simply because the embodiments of the specification do not contain examples explicitly covering the full scope of the claim language. That is because the patent specification is written for a person of skill in the art, and such a person comes to the patent with the knowledge of what has come before. Placed in that context, it is unnecessary to spell out every detail of the invention in the specification; only enough must be included to convince a person of skill in the art that the inventor possessed the invention and to enable such a person to make and use the invention without undue experimentation.

Additionally, the Patent and Trademark Office Board of Patent Appeals and Interferences has stated: "The test [for enablement] is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed to enable the determination of how to practice a desired embodiment of the invention claimed". *Ex parte Jackson*, 217 U.S.P.Q. 804, 807 (1982); *see also Ex parte Erlich* 3 U.S.P.Q.2d 1011 (B.P.A.I. 1982) (observing that although a method might be "tedious and laborious," such

experimentation is nevertheless "routine" defining "routine" experiments as those which use known methods in combination with the variables taught in the patent to achieve the expected, specific, patented result).

It is respectfully submitted that the claimed invention is enabled by the as-filed specification. For example, the as-filed specification clearly teaches how one is to make the claimed polypeptides (see, for example, page 3, lines 10-20; page 9, lines 8-19; page 11, line 24 through page 12, line 16; and Example 1). The as-filed specification also teaches (and the claims recite) the positions of the amino acids that are to be substituted within the claimed MCP proteins as well as the amino acids that should be used in that capacity (see, for example Table 1; page 9, lines 8-19; and page 11, line 24 through page 12, line 16). The as-filed specification also teaches methods of purifying the claimed MCP polypeptides and assays that can be used to assess the ability of the MCP polypeptides to antagonize the activity of unaltered MCP proteins (see, for example, Example 1 and Example 2). Thus, it is respectfully submitted that the as-filed specification enables the claimed invention as it provides the necessary teachings to allow one skilled in the art to practice the claimed invention without undue experimentation and reconsideration and withdrawal of the rejection is respectfully requested.

Claim 76 is rejected under 35 U.S.C. § 112, first paragraph, as nonenabled by the subject specification. The Office Action indicates that the specification is enabled for a host cell in culture transformed with an expression vector comprising a nucleic acid encoding a protein of amino acid sequence set forth in SEQ ID NO: 3 but is not enabled for *in vivo* transfection. The Office Action also states that the specification does not provide any examples that disclose how to make or use host cells that comprise a DNA sequence encoding a protein of amino acid sequences as set forth in SEQ ID NO: 3 in an animal. Applicants respectfully assert that the claims as filed are enabled. Applicants note that it is believed that the Office Action intended to reject claim 70 rather than claim 76. Accordingly, Applicants have amended claim 70 to indicate that the host cells are "isolated" in accordance with the Examiner's suggestion. Reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, first paragraph, is respectfully requested.

Claims 57-83 are rejected under 35 U.S.C. § 112, second paragraph, as indefinite. The rejections will be addressed in the order in which they were presented in the Office Action.

Claim 57 is rejected as being vague and indefinite because it fails to recite a reference SEQ ID NO: for human mature MCP-1 protein and for reciting the phrase "has antagonistic activity to unaltered MCP proteins." Applicants have amended the claims to indicate a SEQ ID NO: for the human mature MCP-1 protein thereby addressing the rejection in this regard. With respect to the issue raised for the phrase reciting "has antagonistic activity to unaltered MCP proteins", Applicants note that the claim has been amended to indicate that the claimed polypeptides antagonize the activity of unaltered MCP proteins. Support for this amendment can be found, for example, at page 32, lines 1-10 of the as-filed application.

Claims 58, 68, 69, 70, 71, and 72 are rejected for reciting the phrase "has antagonistic activity to unaltered MCP proteins." The Office Action indicates that the claimed limitation is improper because the MCP protein is an MCP-1 receptor antagonist not a MCP antagonist. As indicated above, the rejected phrase has been replaced with "antagonizes the activity of unaltered MCP proteins". Thus, it is respectfully submitted that this rejection is now moot.

Claim 63 has been canceled; therefore, the rejection is moot.

Claim 64 is rejected for reciting "MCP proteins". Applicants have amended the claim to recite "MCP protein".

Claim 61 is rejected because it recites "one or more amino acid residues have been added, deleted, or substituted" and there is no upper limit on the number of amino acid residues which have been added, deleted, or substituted. This rejection is moot in view of the amendments made to the claim which indicate that a single amino acid residue has been added, deleted or substituted.

In view of the foregoing comments and amendments to the claims, reconsideration and withdrawal of the rejection under 35 U.S.C. § 112, second paragraph, is respectfully requested.

Claims 57-61, 63-65, 68-76, 78-80 and 83 are rejected under 35 U.S.C. § 103(a) as obvious over Hemmerich *et al.* (1999). The Office Action indicates that Hemmerich *et al.* teach mutations in MCP-1, including single amino acid substitutions at positions 18 or 19, to test the role of the mutations in ligand binding. The Office Action then states that it would have been obvious to one skilled in the art to introduce mutations at both of these positions because the individual mutations produce mutants that have a 2-3 fold decrease in binding affinity for receptor. The Office Action then argues that, on this basis, the skilled person would have expected greater success with the

double mutant. Applicants respectfully assert that the claimed invention is not obvious over the cited reference.

At the outset, it is submitted that Hemmerich *et al.* do **not** describe the claimed MCP-1 double mutants. Rather, Hemmerich *et al.* seek to identify the regions of MCP-1 that contact its receptor, CCR2. For that purpose, all surface-exposed residues were substituted with alanine to analyze the difference in receptor binding (page 13017, left-hand column). Hemmerich *et al.* teaches that the majority of point mutations had no effect on the receptor binding. However, two clusters of primarily basic residues (R24, K35, K38, K49 and Y13) reduced the level of receptor binding by 15- to 100-fold. The paragraph bridging pages 13016 and 13017 shows that mutations in positions 18 **or** 19 only result in a 2-3 fold decrease in binding (see also page 13022, right-hand column and Figure 3). Therefore, the teachings of Hemmerich *et al.* identify residues R24, K35, K38, K49 and Y13 as crucial for the receptor binding whereas and R18 and K19 are not taught to be significantly involved in receptor binding. Indeed, Figure 3 shows these mutations (R18 and K19) having an activity that is not significantly different than the vast majority of the mutants depicted in the Figure. Further, Applicants note that the one protein with multiple mutations in various lysine residues (mutant 1+10-76, 7/9 in Figure 3 having mutations at K19, K35, K38, K44, K49, K56, K58) did not exhibit significant loss of receptor binding affinity (particularly as compared to the single point mutations at R24, K35, K38, K49 and Y13). Thus, it is respectfully submitted that one skilled in the art would not have been motivated to construct a MCP-1 mutein having a double mutation at positions R18 and K19 in view of the teachings of Hemmerich *et al.* Further, in view of the teachings that a MCP-1 protein having multiple point mutations did not have an appreciably different binding affinity for CCr2 receptors, one skilled in the art would not have been motivated to make the substitutions as argued in the Office Action. Accordingly, reconsideration and withdrawal of the rejection is respectfully requested.

Further, even assuming a *prima facie* case of obviousness has been established by the Patent Office, it is respectfully submitted that the claimed polypeptides possess unexpectedly different biological activities as compared to those of the prior art. For example, the double mutants showed similar *in vitro* and *in vivo* chemotactic activity. However, as demonstrated in the Examples, the double mutants disclosed herein exhibited chemotactic activity that was similar to wild-type

polypeptides *in vitro* (see Example 2 and Figure 4). However, this same mutant inhibited/antagonized wild-type MCP-1 activity as measured by recruitment of peritoneal cells (see Example 2 and Figure 5). Further, Proudfoot *et al.* (*Proc. Natl. Acad. Sci. USA*, 2003, 100:1885-1890) indicated that a MCP-1 double mutant R18, K19 failed to recruit intraperitoneal cells when tested at concentrations 10,000 fold higher than wild-type MCP-1 (see *In vitro and in vivo activity of GAG binding site mutants*, pages 1888-1889 and Figure 2). Accordingly, it is respectfully submitted that the claimed MCP proteins exhibit unexpectedly different properties than one skilled in the art would have expected based upon the teachings of Hemmerich *et al.* and the results observed in the *in vitro* chemotactic assays. Thus, the claimed invention is not obvious in view of the teachings cited in the rejection.

Claims 62, 67, 77 and 82 are rejected under 35 U.S.C. § 103(a) as obvious over Hemmerich *et al.* (1999) in view of Capon *et al.* (U.S. Patent No. 5,116,964). The Office Action states that the Capon *et al.* patent teaches chimeric proteins for directing ligand binding partners such as growth factors, hormones or effector molecules to cells bearing ligands for the ligand binding partners comprising a ligand binding partner fused to a stable plasma protein which is capable of extending the *in vivo* half-life of the ligand binding partner when present as a fusion with the ligand binding partner, in particular wherein such a stable plasma protein is in immunoglobulin constant domain. Applicants respectfully assert that the claimed invention is not obvious over the cited references as Capon *et al.* fail to remedy the defects noted in the teachings of Hemmerich *et al.*, as discussed above, and a *prima facie* case of obviousness has not been established. Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested.

Claims 66 and 81 are rejected under 35 U.S.C. § 103(a) as obvious over Hemmerich *et al.* (1999) in view of Hart (U.S. Patent No. 5,094,941). The Office Action asserts that the Hart patent teaches a means of labeling proteins with radioisotopes or imaging agents for diagnostic purposes or for use in assay methods. Applicants respectfully assert that the claimed invention is not obvious over the cited reference. Again, various deficiencies have been noted above with respect to the teachings of Hemmerich *et al.* and these defects are not remedied by the teachings of Hart *et al.* Accordingly, reconsideration and withdrawal of the rejection under 35 U.S.C. § 103(a) is respectfully requested as a *prima facie* case of obviousness has not been established.

It should be understood that the amendments presented herein have been made solely to expedite prosecution of the subject application to completion and should not be construed as an indication of Applicants' agreement with or acquiescence in the Examiner's position. Applicants expressly reserve the right to pursue the invention(s) disclosed in the subject application, including any subject matter canceled or not pursued during prosecution of the subject application, in a related application.

In view of the foregoing remarks and amendments to the claims, Applicants believe that the currently pending claims are in condition for allowance, and such action is respectfully requested.

The Commissioner is hereby authorized to charge any fees under 37 CFR §§1.16 or 1.17 as required by this paper to Deposit Account No. 19-0065.

Applicants invite the Examiner to call the undersigned if clarification is needed on any of this response, or if the Examiner believes a telephonic interview would expedite the prosecution of the subject application to completion.

Respectfully submitted,

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